PATTERNS OF EXTENDED LIPID PROFILE ABNORMALITIES IN CORONARY ARTERY DISEASE PATIENTS OF BUNDELKHAND REGION

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CERTIFICATE

This is to certify that the work entitled "**PATTERNS OF EXTENDED LIPID PROFILE ABNORMALITIES IN CORONARY ARTERY DISEASE PATIENTS OF BUNDELKHAND REGION**" is being submitted as a thesis for M.D. (Medicine) Examination, 2002, Bundelkhand University, has been carried out by **Dr. Deep Chandra Pant** in the Department of Medicine, M.L.B. Medical College, Jhansi.

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INTRODUCTION

INTRODUCTION

Abnormalities in plasma lipoproteins and derangements in lipid metabolism rank as the most firmly established and best understood risk factors for atherosclerosis.

Current national guidelines recommend cholesterol screening in adults. The screening should include a fasting lipid profile (total cholesterol, triglycerides, low density lipoprotein (LDL) cholesterol and high density lipoprotein (HDL) cholesterol.

Studies have shown that apolipoprotein A1: Apolipoprotein B ratio distinguishes unequivocally between patients with and without coronary artery disease (CAD). Therefore apolipoprotein A1 and B studies are superior to conventional total cholesterol or HDL and LDL cholesterol studies for predicting risk of atherosclerosis. It is now proved in case studies that individuals with angiographically confirmed heart disease have significantly lower APO-A1 and higher APO-B levels compared to

normal persons. Apolipoprotein studies have shown promise in improved management of patients of myocardial infarction to reduce the risk of re infarction. Monitoring of patients of coronary bypass surgery with regard to risk and severity of restenosis is substantially better with these studies. On the preventive aspect, cases with family history of coronary artery disease show a higher degree of agreement with apolipoprotein studies than with other lipid parameters. Genetic disorders of lipid metabolism can be recognised at a early stage and corrective measures taken for example, in familial combined hyperlipidemia (responsible for >10% of M.I's) and hyperbetalipoproteinaemia (50% of all CHD patients).

Dietary measures, including specific consultations by practitioners with training in nutrition, should be offered to all patients with hyperlipidemia as defined by the National Cholesterol Education Project Adult Treatment Panel 11:A "normal" total cholesterol level should not

falsely reassure individuals with additional risk factors for coronary heart disease or when HDL level is below 40mg/dl. Many patients with established atherosclerosis fall into this category. Such individuals should receive particular encouragement to adopt life style measures such as diet and exercise aimed at increasing their HDL levels.

The addition of drug therapy to dietary and other non pharmacologic measures to reduce the risk of artherosclerosis events in asymptomatic disease remains unsettled. In asymptomatic patients with heterozygous familial hypercholesterolemia, LDL lowering by pharmacologic measures reduces atherosclerosis in both men and women. The west of Scotland study established that lipid lowering with the HMG-CoA inhibitor pravastatin can effectively reduce cardiac events and total mortality in a cohort of patients with hypercholesterolamia but without prior myocardial infarction. The recent AFCAPS/TEX CAPS study showed that treatment

with Lovastatin similarly reduces coronary events in patients without previous myocardial infarction but with "average" total and LDL cholesterol levels and somewhat decreased HDL levels.

Although the role of drug therapy in primary prevention of the manifestations of atherosclerosis remains incompletely defined abundant evidence establishes the benefit of drug therapy in patients with hypercholesterolemia and established coronary artery disease. A number of well designed and executed large scale clinical trials have now shown that treatment with statins reduces recurrent myocardial infarction, reduces strokes and lessens the need for revascularization or hospitalization for unstable anginapectoris. These studies have enrolled patients in numerous countries of atleast three continents and encompass individuals with clearly elevated levels of cholesterol and those with "average" total and LDL cholesterol levels.

Lipid lowering therapies do not appear to exert their beneficial effect on cardiovascular events by

causing a marked "regression" of obstructive coronary lesions. Angiographically monitored studies of lipid lowering have shown at best a modest reduction in coronary artery stenosis over the duration of study. Yet the same studies consistently show substantial decreases in coronary events. These results suggest that the mechanism of benefit of lipid lowering does not require a substantial reduction in the fixed stenosis. Rather, the benefit may derive from "stabilization" of atherosclerosis lesions without decreased stenosis. Such stabilization of atherosclerotic lesions and attendent decrease in coronary events may result from egress of lipids or by favourably influencing aspects of the biology of atherogenesis. In addition, as sizeable lesions may protude abluminally rather into the lumen, shrinkage of such plaques might not be apparent on angiograms.

The benefit of LDL lowering by HMG-CoA reduction inhibitor (statin) therapy or cardiovascular events seems to require 6-24 months

of treatment. Improvement of vasomotor responses to endothelial dependent vasodilators occurs much more rapidly, requiring 6 months or less the HMG-CoA reductase inhibitors may act by two or more mechanism on the arteries of hypercholesterolemic individuals the relatively rapid improvement in endothelial dependent vasodilation may reflect enhanced production or reduced destruction of the endogenous vasodilator nitric oxide at the level of the arterial endothelium. Reduction in the thrombotic complications of atherosclerosis, such as myocardial infarction or unstable angina, probably require more prolonged treatment to effect removal of lipid from deeper within atheroma yielding improvements in the biology underlying plaque destablization.

Our current understanding of the mechanisms by which elevated LDL levels promote atherosclerosis relates to oxidative modification of these particles within the artery wall, promoting formation of macrophage-derived foam cells and providing a

stimulus for inflammation. These concepts have given rise to consideration interest in the possibility that antioxidants, either dietary or pharmacologic might reduce atherogenesis. Considerable experimental evidence supports this notion. In addition, may observational studies show a correlation of antioxidant consumption and reduced cardiovascular risk. Rigorous controlled clinical trial evidence, however has not yet proven the effectiveness of antioxidant therapy, whether dietary or with supplements of vitamin or drug, for prevention or treatment of atherosclerosis. Indeed, controlled trials with β-carotene have demonstrated no reduction in cardiovascular events. For these reasons, as its efficacy remains speculative, it is premature to consider antioxidant administration as are placement for established therapies. Furthermore, general use of such treatments, particularly in lower risk individuals should await the results of rigorous prospective studies designed to define the doses, appropriate patient groups, and

evaluate the possibility to adverse or unwanted effects of antioxidants.

A study of lipid levels in Indian patients with coronary artery disease was done by Krishnaswamy et al. In this a detailed cross sectional analysis of total cholesterol and triglyceride levels was studied in 1066 consecutive male patients who underwent selective coronary arteriography to confirm or exclude coronary arterial disease. There were 877 cases of coronary arterial disease and 189 patients with normal coronary arteries. Besides descriptive statistics of lipid levels in different age groups, percentile distribution was studied. Association characteristics between lipids and other risk factors was studied by multiple regression analysis. Relative risk of lipids, controlling for the confounding variable of age as well as weight was obtained using Mantel Haenzel Chi Square procedure. Results revealed the occurrence of coronary artery disease with low lipid-levels in our population. The 50^{th} percentile for total cholesterol

was 205mg/dl for the cases and 186mg/dl for controls, while triglyceride it was 158mg/dl for cases and 140mg/dl for controls. Multiple regression analysis of smoking, positive family history, diabetes, hypertension, weight and age contributed to a low R square value of 2.49% for cholesterol and 4.22% for triglycerides in case and controls. The Mantel Haenzel Chi Square test procedure confirmed that low lipid level could be seen irrespective of age or weight of individuals. It is speculated that other factors which include ageing, metabolic or immunologic components yet to be ascertained, could contribute additionally, to atherosclerotic coronary artery disease in our population.

AIMS AND OBJECTIVES

AIMS AND OBJECTIVES

To study the patterns of extended lipid profile abnormalities in coronary artery disease patients of Bundelkhand region.

REVIEW OF LITERATURE

REVIEW OF LITERATURE

Levels of lipid in the blood of patients with coronary artery disease have received considerable attention over the years. The gist of these studies have been summed up by stamler in his report where he has claimed that "the relationship between serum cholesterol and coronary heart disease is not a threshold one but a continuous graded one that powerfully affects risk for the great majority of aged men.

While large populations studies on lipids have been reported from Europe, Japan, Puerto Rico it was considered timely that this aspect of coronary artery disease be made available to the International Medical Community.

Coronary artery disease (CAD) is the most common cause of mortality and morbidity in the western world, and is rapidly becoming a common malady in other parts of the world. Fortunately, mortality from CAD in the USA has declined by

about 50 percent in the last two decades, however, the decline has been much less in the European countries and there is a rising epidemic of coronary artery disease in Indian population.

The decline in CAD-related morbidity and mortality in the west has been attributed to the control of risk factors and development of preventive and therapeutic strategies. The latter includes frequent use of pharmacological agents, such as aspirin, beta-adrenergic antagonists, lipid lowering agents and angiotension-converting enzyme inhibitors. Evolution of coronary artery bypass surgery and intracoronary procedures has also been very beneficial in select group of patients.

The cause of atherosclerosis, which is the primary underlying pathologic basis of CAD, remains elusive inspite of work done in many laboratories around the world. Atherosclerosis begins in teens , the atheroma enlarges with age, and in later stages. The proximate cause of acute coronary syndromes (unstable angina and acute

myocardial infarction) is instability of atherosclerotic plaque and its rupture, which facilitates formation of a platelet-initiated occlusive thrombus in the narrowed coronary artery. These clots from repetitively in the atherosclerotic arteries, as evident from autopsy studies in patient dying of acute myocardial ischaemia. Increase in shear stress, vasospasm and inflammation in the atherosclerotic region may be the basis of plaque instability, but the precise sequence of events leading to acute thrombus formation which leads to morbid and fatal events remains far from clear.

In the context of atherogenesis, epidemiologists, clinicians and researchers continue to examine the role of several conditions associated with atherosclerosis and thrombosis as well as with post-event outcome. This work reviews the role of traditional and emerging risk factors in atherosclerosis in general and CAD in particular.

Role of traditional risk factors

Epidemiological studies beginning primarily in the US in the 1950s and later in Europe and elsewhere have identified several risk factors that are associated with evolution of CAD and its manifestations. These risk factors may be classified as 'unmodifiable' e.g., age, male sex, post menopausal state in women and positive family history)) or 'modifiable' (e.g, hypercholesterolemia, smoking, diabetes, hypertension, obesity and sedentary lifestyle). These risk factors appear to increase the risk of CAD related event in a synergic fashion. Identification of these risk factors has led to strategies directed at their recognition and modification. This information has been widely disseminated to physicians and the general public by government and professional organisations (such as the American Heart Association and the American College of Cardiology).

The pharmacological industry has develop a host of drugs to treat many of these risk factors. While a detailed description of pharmacological strategy is

beyond the scope of this work, drug induced modifications of CAD risk factors has been beneficial only in some conditions. For ex., aggressive reduction of cholesterol levels with HMG CoA reductase inhibitors has had a very positive effect on CAD related morbidity and mortality in both primary and secondary prevention trials. Pharmacological lowering of blood pressure has been effective in reducing the incidence of stroke but it has had only a marginal effect in reducing CAD related events. Controls of blood glucose by conventional drugs similarly reduces the number of hyper and hypoglycemic events, but has a little effect on the progression of CAD. Lifestyle modification with cessation of smoking and inclusion of physical activity (exercise) has had a positive impact on CAD related morbidity and mortality in both, its prevention and treatment. In the US, there has been a steady, but modest decline in serum cholesterol levels over the last 20yrs. similarly, the incidence of smoking has somewhat

decreased over this period. Both these factors have contributed to a reduction in CAD related morbidity and mortality.

Role of emerging risk factors

While the traditional risk factors are associated with development of CAD, a substantial number of CAD patients do not have identifiable traditional risk factors. In addition, a large number of subjects with conventional risk factors do not develop significant CAD. These observations have led to recognition of certain other factors that may be relevant in patients who suffer from CAD without traditional risk factors;. Further, CAD may be related to different aetiologies in different patients and populations. It is unlikely that a disease, which affects a third of the world population can be explained on the basis of 5-10 risk factors. The role of certain new risk factors has been described here

Lipid disorders

Low HDL cholesterol levels: Until recently, emphasis has been placed on CAD risk related to high serum levels of total and LDL cholesterol. A critical review of literature shows that low serum levels of HDL cholesterol may have a very important predictive value in the development of CAD. This is particularly true in women, who generally have high levels of HDL cholesterol until they reach menopause, when the levels of HDL cholesterol begin to decline and the incidence of CAD starts to increase. This has led to the inference that a decline in estrogen levels is the cause of age related decreases in HDL cholesterol values. Low HDL cholesterol level in serum has been observed frequently in young patients (mainly men) with CAD, and may be a more important risk factors that high levels of total or LDL cholesterol

Hypertriglyceridemia : Epidemiologic studies have also shown hypertriglyceridemia to be an important risk factor in CAD. Hypertriglyceridemia is often

observed with low HDL cholesterol levels, and it had been difficult to separate the role of these two factors. Nonetheless, some studies have shown independent risk of persistent hypertriglyceridemia. Earlier, an independent relationship of triglyceride levels with the fast acting plasminogen activator inhibitor (PAI-1) was established in patients with CAD. This may be a link between triglyceridemia and thrombosis. However, there are frequent and marked variations in serum triglyceride levels, and a carbohydrate rich diet can lead to a marked rise in serum triglyceride levels diabetics often have hypertriglyceridemia. It is inferred that low HDL cholesterol and hypertiglyceridemia are frequently associated with IGT in the young and in most CAD patients from Indian subcontinent, which may reflect a unique metabolism disorder consisting of hyperinsulinemia and diabetes mellitus.

Lipoprotein(a) Lp(a) : Lp(a) is an LDL like particle with apolipoprotein(a) attached to apolipoprotein β through disulphide bonds. It has structural homology

to plasminogen with which it competes for cell surface bindings. By displacing plasminogen, it reduces formation of endogenous tissue plasminogen activator (TPA). Thus, reduction in TPA levels may be how elevated levels of LP(a) confer risk of thrombosis and atherosclerosis. A number of studies have linked elevated levels of Lp(a) to the risk of CAD, especially when associated with elevated LDL cholesterol or low HDL cholesterol levels.

Insulin Resistance syndrome : This syndrome is characterised by the presence of hyperinsulinemia, central obesity, hypertriglyceridemia, low levels of HDL cholesterol, diabetes mellitus (or euglycemia), hypertension and CAD. Whether this syndrome, first described by Reaven is a unique genetically linked metabolic syndrome or a combination of commonly observed accompaniment of CAD is not well defined. However this pattern is not infrequently observed in middle aged or elderly CAD patients.

Thrombogenic factors

Hyperfibrinogenemia : Fibrinogen increases blood viscosity and risk of thrombosis- a proposed link to atherosclerosis. Several epidemiologic studies have shown that high fibrinogen are associated with increased incidence of CAD. A meta-analysis based on 12 population based studies and six studies in patients with pre-existing vascular disease suggests a strong association (RR of highest to lowest tercile) between fibrinogen levels and CAD risk, as well as the role of fibrinogen in predicting outcome of patients with CAD. However, fibrinogen levels show marked inter laboratory, genetic, racial, gender and seasonal variations. Fibrinogen is an acute phase reactant; its value rises in all acute and inflammatory conditions and its levels are particularly high in smokers. Fibrinogen levels are low in women, who generally have lower incidence of CAD. Failure of modification of fibrinogen levels to show clinical benefit also discourages the measurement of fibrinogen in all CAD patients as a

prognostic indicator. Several fibrinogen gene polymorphisms associates with elevated fibrinogen levels have been described. Much work is being done in studying the role of fibrinogen gene polymorphism in determining elevated fibrinogen levels and the risk of CAD.

Isolated low high density lipoprotein cholesterol

Isolated low high HDL-C is a unique but not an uncommon lipid abnormality, defined as HDL-C level below 35mg/dL with total cholesterol, as well as triglyceride less than 200mg/dl. in a fasting blood sample. Several observational studies have shown that reduced plasma level of HDL-C is a strong independent predictor of CHD. It has been suggested that for every one mg/dL decrease in HDL-C the risk for CHD is increased by 2-3%.

The NCEP has recommended that HDL-C should be measured in addition to total cholesterol at least once in five years in all individuals aged 20yrs and above. In those found to have isolated low HDL-C,

the primary goal of therapy should be the control of other risk factors for CHD. In patients receiving statin therapy, a low level of HDL-C denoted increased risk of recurrent coronary morbidity. For the modification of low HDL-C related risk, it is recommended to initially lower LDL-C to target levels and if HDL continues to remain below 35mg/dL, niacin therapy is given for the secondary prevention of CHD. Niacin can increase HDL-C by 15-35% and decrease LDL-C by 10-25% in a dose of 1.5-3g/day. However, side effects such as flushing and vasomotor symptoms can be reduced by administration of a time release preparation at night alongwith aspirin. Fibric acids have also been shown to increase HDL-C when combined with a statin; however, this combination therapy can cause serious side effects such as myositis.

Hypertriglyceridemia

The association between hypertriglyceridemia (HTG) and atherosclerosis is still controversial though epidemiolgic studies have shown HTG to be

an important risk factors in CAD. HTG is often observed with low HDL-C, and it has been difficult to separate the role of these two factors. The key issue is whether HTG is directly responsible in the causation of atherosclerotic heart disease or is merely a marker for a cluster of cardiovascular risk factors, often termed as 'metabolic syndrome'. Although an initial meta-analysis challenged the role of HTG as an independent risk factor, several recent studies have highlighted its independent significance in the aetiology of CHD.

In the Coronary Drug Project (CDP) conducted on more than 800 male survivors of myocardial infarction (MI), the group which received niacin had 26% reduction in triglycerides with 27% decrease in recurrent CHD events. In the statin trials for primary and secondary prevention of CHD, there was an overall 10-15% reduction in triglycerides levels. Statin therapy effectively reduced CHD events in patients with LDL less than 130mg/dl, even when triglyceride levels were mild to moderately elevated.

This emphasized that LDL reduction was the primary goal in hyperlipidemic patients with normal or elevated triglyceride levels.

The role of fibric acids in triglycerides reduction has been studied in some recent trials. The Bezafibrate infarction Prevention trial (BIP) randomised 3122 middle aged men and women with CHD to Bezafibrate versus placebo. There was 25% decrease in TG, 10% increase in HDL-C, and 5% decrease in LDL-C levels following bezafibrate therapy. While there was an insignificant reduction in the primary end point of non fatal MI and cardiovascular deaths, this was reduced by 40% in the group with triglyceride levels more than 200mg/dL. In the VAHIT trial, gemfibrozil produced a 30% reduction in triglyceride, 6% increase in HDL-C level and a significant reduction in CHD event rate. Precise explanation for the difference in the results of the two trials are not known. Besides others one of the explanations for the variance in the results of these two trials could be the

difference in the effects of two drugs beyond their class effect. The recently concluded Diabetes Atherosclerosis Intervention Study (DAIS) found that in type II diabetes mellitus, micronised fenofibrate reduced angiographic progression of atherosclerosis by 40% in association with a reduction events by 23%.

In conclusion, fibrates are the most potent triglyceride lowering agents producing a reduction of 20-55%. Statins also are able to lower triglyceride by upto 30% in patients with levels above 200mg/dL.

Lipoprotein(a)

Lipoprotein(a) is a LDL like protein having structural homology to plasminogen. It contributes to CHD events through its direct atherogenecity, as well as enhanced thrombogenesis. In Indians Lp(a) level of more than 22mg/dL has been shown to be an independent risk factor for premature CHD. Elevated Lp(a) is most predictive of CHD when associated

with increased LDL-C and the adverse effects of both are neutralised when LDL-C alone is lowered.

There are no prospective primary or secondary prevention trials aimed at reducing CHD events by modifying Lp(a) levels. Therefore, the clinical utility of Lp(a) estimation as part of screening lipid profile is unknown, but may be useful in making treatment decisions in specific cases. In patients of CHD with LDL-C between 100-130mg/dL despite lifestyle modification, a high Lp(a) level may be warrant the use of statins to reduce LDL-C below 100mg/dL. In individuals with a strong family history of CHD and LDL-C between 130-160mg/dL, an elevated Lp(a) suggests the need for instituting pharmacologic therapy with nicotinic acid or a statin, with the primary objective of reducing LDL-C below 130mg/dL. Statins and resins did not prove effective in reducing Lp(a), but a high dose of nicotinic acid (4gm/day) has been shown to lower Lp(a) by approximately 40%. It can also be lowered

by neomycin, certain steroids such as stanozolol, n-3 fatty acids and possibly, fenofibrate.

MISCELLANEOUS RISK FACTORS FOR CAD

Factors VII and other procoagulants : Factor VII is a vitamin K dependent procoagulant factor, and its high levels are associated with CAD in prospective observational studies. Its levels are influenced by dietary saturated fat intake and by estrogen use. Other haemostatic factors that have been casually linked to CAD include PAI-1, TPA antigen, Won Willebrand factor, proteins C and S, anti-thrombin III levels. Deficiencies in anti-thrombin III & proteins C & S correlate with thrombotic tendency, more conclusively for venous rather than arterial disease. Elevated PAI-1 levels have been shown to correlate with acute myocardial infarction in young, who also have hypertriglyceridemia and low HDL- cholesterol values.

Unfortunately, the high cost associated with measurement of these procoagulants (including fibrinogen) and lack of specific therapy precludes recommendation of measurement of these variables in all subjects, except those in whom traditional risk factors do not explain the presence of CAD characterised by repetitive thrombotic tendency.

Increased platelet Aggregation : Abnormally increased platelet aggregation was first described over 20yrs ago in patients with CAD. Subsequently several investigators showed increased platelet aggregation occurring spontaneously or in response to conventional stimuli in a cross section of patients with CAD as well as in CAD prone subjects. This concept is consistent with the hypothesis of platelet initiated thromboatherosclerosis. The beneficial effect of platelet inhibition with aspirin in primary and secondary prevention trials has been conclusively shown. However, the benefits of aspirin may not be entirely related to its platelet

inhibitory effects, but also to its anti-inflammatory properties.

Table : New risk factors in Atherosclerosis & CAD

1. **Lipid Disorders**
   a. Low HDL levels
   b. Hypertriglyceridemia
   c. Lipoprotein(a)
2. **Thrombogenic Disorders**
   a. Hyperfibrinogenemia
   b. High levels of factors VII & other procoagulants
   c. Increased platelet aggregation
3. **Psychosocial Factors**
   a. Depression
   b. Anxiety
   c. Loss of hope or social isolation
4. **Miscellaneous**

a. inflammation and infection

b. iron load

c. abnormalities in renin-angiotensin system

d. left ventricular hypertrophy

e. oxidation-antioxidation imbalance

f. hyperhomocyteinemia

Psychosocial factors

A number of psychosocial factors, depression, anger, hostility, anxiety, loss of hope and social isolation, have been associated with the development of CAD and cardiac arrhythmias as well as with outcome after CAD events. Psychosocial stress and hostility are emerging as significant factors. Social factors, such as low educational level and socioeconmic standard, are also related to an increased risk of CAD in observational studies. Increased CAD risk has not been conclusively associated with type A personality, as initially believed.

Major depression, frustration and social isolation increase the risk of mortality after acute myocardial infarction independent of other variables, such as extent of CAD, heart failure, comorbid conditions and age.

Psychosocial factors could mediate CAD and the risk of acute cardiac events via neuroendocrine mechanisms. Changes in plasma and brain catecholamines and serotonin during physical psychosocial stress may enhance platelet aggregation and coagulants (thrombosis and decreased oxygen supply) thus raising the blood pressure and heart rate (increase in oxygen demand). Increased shear stress in the atheromatous region during pychosocial stress may be the cause of plaque rupture, resulting in acute thrombosis and its sequelae (unstable angina, acute myocardial infarction and coronary artery reocclusion after PTCA). Psychosocial and mental stress have also been shown to cause silent ischemia, presumably by induction of spasm of atherosclerotic arteries. In

addition, psychosocial stress leads to poor compliance with therapeutic modalities and reduced visits to health care providers.

Can interventions to modify psychosocial factors improve outcome after CAD events? Can they be used as a preventive measure? Early studies have been shown promising results. Psychosocial interventions which include social and emotional support, education about CAD and reinforcing healthy behaviour, are associated with reductions in psychologic distress, heart rate and systolic blood pressure. Further, the benefits are over and above those achieved by medication and exercise, both in terms of improved quality of life as well as reduced mortality. However, a basic problem in interventional studies is the definition of stress. What is stressful to one person may be pleasurable to another. Psychological descriptors of stress are subjective. We perhaps need to individually tailor the intervention in order to lead to the greatest benefits. Given the apparent overall benefit for

psychological interventions, more work is needed to identify which patient is likely to benefit most from a specific treatment.

Miscellaneous Risk Factors

Inflammation and Infection : There is evidence of persistent inflammation in atherosclerotic coronary arteries. Accumulation of lymphocytes is often observed n the shoulder region of atheroma, and it has been suggested that acute increase in inflammatory load may lead to instability of the plaque. Inflammation is also observed in the coronary arteries and myocardinal soon after dissolution of the occlusive thrombus. Serologic studies in patients with CAD show evidence of shedding of endothelial adhesion molecules and their counterligands. What leads to inflammation is not clear, but may include infections, oxidised lipids, free radicals and products of renin-angiotensin system.

The infectious theory of atherosclerosis has shown resurgence based on the demonstration of viral particles (cytomegalovirus and herpes simplex virus) and common bacteria (mainly chlamydia pneumoniae) in the atherosclerotic regions. Current interest has focused on ongoing infection with C. pneumoniae as a pathologic basis of atherogenesis in some genetically-predisposed individuals, especially those with HLA-DR genotypes 12 & 15 or 17, and high levels of Lp(a). The subject of inflammation and infection in the genesis CAD has been reviewed. Although preliminary studies suggest benefit of anti-infective therapy, this issue is far from well defined, and the role of antibiotics is not established in the therapy of CAD.

Iron load : Some early cross-sectional reports indicated excess iron load as risk factor in CAD. Iron is an important trace metal necessary as a catalyst for generation of free radicals which, as discussed below, have been implicated in endothelial dysfunction and atherosclerosis.

However, detailed analysis of these studies has now shown a lack of significant relationship between iron in the body and CAD.

Abnormalities in Renin-Angiotensin System, (RAS): Various clinical and cross sectional studies have shown involvement of RAS in atherogenesis. Subjects with raised renin, aldosterone and angiotensin II levels appear to have greater incidence of CAD, its sequelae, and poor prognosis after CAD related event. Therapy with RAS blockers has clearly shown to significantly reduce morbidity and mortality after acute myocardial infarction. Certain ACE gene polymorphisms are associated with increased ACE activity, and in early studies these gene polymorphisms were shown to be strong predictors of CAD. Subsequent studies, however, failed to show similar consistent relationships. Work on type I angiotensin II receptor polymorphisms as possible predictors of CAD and related events is currently underway in several laboratories.

Left Ventricular Hypertrophy (LVH) : LVH determined by ECG or echocardiography was shown to be independent risk factor for CAD and its sequelae in the Framingham study data base. This risk is most likely conferred by relative myocardial ischemia as coronary blood flow may not be adequate to meets the oxygen demands of hypertrophied myocardium. Based on this concept, strategies that limit or cause regression of LVH (almost all anti-hypertensive except direct vasodilators) are recommended in patients with syndrome X or hypertension.

Oxidation-Antioxidation Imbalance : There has been renewed interest in excess oxidation as a key player in atherosclerosis. Oxidant species or free radicals are molecules with an extra electron that make them unstable. Free radicals directly injure endothelium, cause breakdown of the vasodilator species nitric oxide and induce platelet aggregation and vasopasm. Generation of free radicals has been incriminated in "reperfusion injury" as well as an

oxidative modification of LDL-cholesterol. The endogenous stores of antioxidants, superoxide dismutase and vitamins C and E, are low in patients with atherosclerosis. Further, observational studies show decrease in CAD risk in men and women taking large amounts of vitamin E. Based on these considerations, studies have been designed to understand the role of dietary supplementation with chain breaking anti-oxidant vitamin C & E. An early study showed a marked reduction in CAD morbidity in patients who were given vitamin E 400-800 units/day in addition to routine conventional drug therapy. However, the precise role of "oxidant-antioxidant imbalance" is not clear, and the AHA/ACC task force currently recommends consumption of fresh foods and vegetables, which are rich sources of natural vitamins and flavanoids.

Hyperhomocysteinemia : Elevated plasma levels of homocysteine, a product of methionine metabolism, are associated with a modest increase in the risk of CAD. Case control and prospective

studies have provided evidence for an independent relationship between hyperhomocysteinemia and vascular disease. Hyperhomocysteinemia also increases mortality risk after acute myocardinal infarction. Mild to moderate elevations in homocysteine levels are due to nutritional deficiency (low intake of folate, vitamin B_6 & B_{12}) or genetic abnormalities involving methylene tetrahydrofolate reductase enzyme. In some subjects, hyperhomocysteinemia may be uncovered after challenge with methionine. Homocysteinemia confers risk for vascular disease secondary to its injurious effect on endothelial cells and pro-platelet aggregatory, pro-oxidant and mitogenic effects. However, not all prospective studies have supported relationship of plasma homocysteine levels and CAD.

Routine monitoring of plasma levels of fibrinogen is not recommended, except in a rare young CAD patient with strong familial history of thrombosis. It may be advisable to increase intake

of healthy foods in all CAD patients, and to prescribe folic acids and vitamins B6 and B12 to subjects at high risk of developing CAD or young patients with pre-existing CAD.

S.S. Krishanaswami[5] *et al did* a detailed cross sectional analysis of total cholesterol and triglyceride levels on 1066 consecutive male patients who underwent selective coronary arteriography in their centre to confirm or exclude coronary artery disease. There were 877 cases of coronary arterial disease and 189 patients with normal coronary arteries. Besides descriptive statistics of lipid levels in different age groups, percentile distribution was studied. Association characteristics between lipids and other risk factors was studied by multiple regression analysis. Relative risk of lipids, controlling for the confounding variable of age as well as coronary artery disease was obtained using the Mantel Haenszel Chi square procedure. Results revealed the occurrence of coronary artery disease with low lipid

levels in our population. The 50th percentile for total cholesterol was 205 mg/dl for the cases and 186 mg/dl for the controls, while for triglycerides it was 158 mg/dl for cases and 140mg% for controls. Multiple regression analysis for smoking, positive family history, diabetes, hypertension, weight and age contributed a low and square value of 2.49% for cholesterol and 4.22% for triglycerides in the cases and controls. The Mantel Haenszel Chi square test procedure confirmed that low lipid levels could be seen irrespective of the age or weight of individuals. It is speculated that other factors which may include, ageing, metabolic or immunologic components yet to be ascertained, could contribute additionally to athrosclerotic coronary artery disease in our population.

Another study by *Aleyamma Joseph and V Raman Kutty*[9] *et al did an* analysis of serum lipids and other risk factors for coronary heart disease in Thiruvanthapuram city. In their study the serum lipid profile and prevalence of other risk factors for

coronary heart disease in residents of an urban housing settlement in Thiruvanthapuram , fasting blood samples was collected from 206 (64%) residents above age 19yrs. and analysed for plasma glucose and various fractions of serum lipids. A detailed questionnaire on the clinical profile and history of the subjects and measured weights and heights was also measured. Mean serum cholesterol was 223.7±44.9 mg% among males and 223.7±45.8mg% among females. Mean high density lipoprotein cholesterol was consistently higher in females in all age groups, while mean low density lipoprotein cholesterol was higher in males till age 40-49 after which the pattern was reversed. Mean total cholesterol in the age range 35-64, after standardisation, was 229.4mg%. Mean serum total cholesterol was higher in this sample when compared to US population, as well as north and west Indian populations. Other risk factors such as high blood pressure obesity, diabetes, sedentary life

style and smoking also had high prevalence in this population.

Anoop Misra, R. Bhasker Reddy, Alladi Mohan et al[8] *studied the pattern of risk factors* in young (<40yrs) North Indian patients with coronary heart diseases. The found a clustering of impaired glucose tolerance, hyperinsulinemia and dyslipidemia in these patients. In their preliminary case control study, 44 young patients (age <40yrs) with coronary artery disease (angina, myocardial infarction), not previously diagnosed to have diabetes mellitus, were recruited seven days to six weeks after the cardiac event (group I), and compared to 20 healthy subjects (group II). After recording history and anthropometric data, they were subjected to oral glucose tolerance test. Each group was divided into A and B subgroups according to the magnitude of impaired glucose tolerance. Hypertension was recorded in 11 (25%) patients in group I, while all the subjects in group II were normotensive ($p<0.05$). Groups IB and IIB consisting of subjects with

impaired glucose tolerance displayed significantly high post load blood glucose levels. After excluding patients with family history of diabetes mellitus, there were 13 (39%) ad 3 (17%) patients with impaired glucose tolerance in group I and II respectively. Total cholesterol and low density lipoprotein cholesterol levels were higher in group I as compared to group II ($p<0.01$). Group IB showed highest mean values of total cholesterol, triglycerides, low density lipoprotein cholesterol and lowest level of high density lipoprotein cholesterol as compared to other subgroups. The study demonstrated significantly high prevalence of hypertension, obesity, impaired glucose tolerance, hyperinsulinemia and dyslipedemia, suggesting fully developed metabolic insulin resistance syndrome in young north Indian patients with manifest coronary heart disease.

Department of Cardiology and Cardiac-biochemsitry laboratory, AIIMS did a study of apolipoprotein(a) polymorphism and its association

with plasma lipoprotein(a) levels. This study indicated a strong associated of elevated plasma lipoprotein(a) concentration with coronary artery disease. An inverse correlation was seen between lipoprotein concentration and isoform size both for the pentanucleotide repeat polymorphism and kringle-4 type 2 polymorphisms.

The Quebec Cardiovascular study provided the strongest evidence that increased levels of fasting plasma apolipoprotein B levels and insulin levels strongly predicted CAD.

Gupta R, Kaul V, Prakash H, Singhal S, Gupta VP et al[6] *at Department of Medicine and Pathology, Monilek Hospital and Research Centre, Jaipur* did a population based case control study of lipid abnormalities in coronary heart disease. A total of 635 newly diagnosed patients with coronary artery disease (518 males and 117 females) and 632 subjects (346 males and 286 females) obtained from an ongoing urban coronary heart disease risk factor epidemiological study were evaluated. Age specific

lipids values (total cholesterol, low density, lipoprotein, high density lipoprotein, triglycerides and total high density lipoprotein cholesterol ratio) were compared using the t-test. Age adjusted prevalence of dyslipidemia as defined by the US National Cholesterol Education Programs was compared using the Chi-Square test. In all the age groups, and in both males and females, levels of total and low density lipoprotein cholesterol were not significantly different. In males, the high density lipoprotein cholesterol was significantly lower in patients with coronary heart disease as compared to controls in all age groups. An age adjusted case control comparison showed that the prevalence of hypertension, diabetes. High total cholesterol (≥200mg%) (males 48.8% Vs 20.2%, females 59.8% Vs 33.4%) and high low density lipoprotein cholesterol (≥130mg/dl) (males 42.1% Vs 15.0%, females 52.1% Vs 31.0%) was significantly more in cases than in controls. The prevalence of low HDL (<35mg%) (males 39.6%

Vs6.2%; females 39.3% Vs 9.5%) high total: high density lipoprotein ratio (>5.0) and triglycerides (≥200mg%, males 39.6% Vs10.2%; females 17.1% Vs 11.9%) was significantly higher in cases ($p<0.05$).

Apolipoprotein A1 and B : Suggested risk levels for coronary heart disease (CHD)

Risk	Apo A1-Apo B ratio
High	0.00-0.50
Moderate	0.51-1.00
Average	1.01-1.50
Low	1.51-5.00

Studies have shown that ApoA1:ApoB ratio distinguishes unequivocally between persons with and those without CHD. Therefore, apolipoprotein A1 and B studies are superior to conventional, Total cholesterol, HDL and LDL cholesterol studies for predicting risk for atherosclerosis. It is now proved in case control studies that individuals with

angiographicaly confirmed heart disease have significantly lower ApoA1 and higher ApoB levels compared to normal persons. Apolipoprotein studies have shown promise in improved management of patients of Ml to reduce the risk of re-infarction. Monitoring of patients of coronary bypass surgery with regard to risk and severity of restenosis substantially better with these studies. On the preventive aspect, cases with family history of CHD show a higher degree of agreement with apolipoprotein studies that with other lipid parameters. Genetic disorders of lipid metabolism can be recognised at a early stage and corrective measures taken.

The apolipoprotein studies have been used in the following cases :

1. To assess the atherosclerotic risk and classify broderline cases not detected during routine cholesterol studies.

2. To recognise genetic disorders of lipid metabolism as in cases of familial combined hyperlipidemia where cholesterol and triglyceride levels are normal but ApoB is elevated. Similarly in hyperapobeta-lipoproteinemia LDL levels are normal but APOB is elevated.

3. To improve the management of myocardial infarction patients and reduce risk of reinfarction.

4. To monitor the patients of coronary bypass surgery with regard to risk and severity of restenosis.

5. To follow up persons with a family history of coronary artery disease as a preventive measure.

Lipoprotein (a)

Lipoprotein(a) or Lp(a) was dicovered as a genetic mutant of low density lipoprotein (LDL) in1963 by Berg, a Norwegein geneticist Lp(a)

consists of two different components, the apolipoprotein B-100 which is component of LDL, and a glycoprotein, the apolipoprotein (a) or Apo(a). Apolipoprotein B-100 and Apo (a) are linked by a disulphide bond. Lp(a)is homologous to plasminogen. In consideration to this similarly in structure, it was proposed that Lp(a) has a relationship with a atherosclerosis, since as a consequence, it can competitively inhibit the action of plasminogen and possibly trigger atherogenic effects. Cholesterol is one of the diagnostic for atherosclerosis. Lp(a) is considered another risk factor which is independent by cholesterol. The individual concentration of Lp(a) in serum depends on genetic factors and therefore the range of variation in a population is relatively large. Starting at concentration of about 30mg/dl of Lp(a) the atherogenic risk is elevated, especially in the persons with concurrently elevated levels of LDL. Lp(a) is therefore one of the best discriminators of atherosclerosis and myocardial infarction. The

concentration of Lp(a) are not influenced by diet or by commonly used lipid depressant drugs. However the Lp(a) levels be lowered by the use of Niacin (vitamin B_3), exercise, neomycin and estrogen replacement therapy. In persons with elevated levels of Lp(a) attention must be paid to other risk factors also.

Suggested use of Lp(a) as a marker for assessment of risk for cardiovascular disease (CVD)

Adult level	**Interpretation**
0-30mg/dl	Desirable
>30mg/dl	Increased risk for CVD
upto 4 fold increase	End stage renal disease
upto 7 fold increase	Nephrotic syndrome

Studies of lipoprotein(a) and apolipoproteins A1 and B

Jacob Jose et al[10] *looked* at CAD in South Indian type 2 diabetic patients and controls in relation to Lp(a) using the Macra Lp(a) kits. They found Lp(a) levels to be a strong and independent risk for CAD.

The risk of CAD increased with every quartile of Lp(a)-levels greater than 50mg/dl. Logistic regression analysis indicted that Lp(a) was an independent risk factor for CAD, stronger than the conventional lipid parameters.

Several recent studies have shown that Lp(a) level are elevated in Indians living in India an abroad. These studies string suggest that the premature CAD in Indians may be genetically determined and that elevated Lp(a) levels may least in part explain the high prevalence of CAD seen Indians. On the other hand, Chinese, Malays and other ethnic groups with low CAD rates have low Lp(a) levels.

A study[7] *conducted by Cherny Z Chuang, PN Subramanium et al at Louisiana state University, USA* was done on 110 Asian Indian Physicians living in USA. They found that lipoprotein(a) (mean =20mg/dl), low density lipoprotein cholesterol, and diabetes (prevalence 7.5%) are more important risk factors for CAD, but bot smoking, when compared to

other Americans. There was no significant difference in lipid levels of vegetarians and non-vegetarians.

Rajeev Gupta, Shipa kastia, Shewata rastogi, EA Enas[6] *of Monilek Hospital and Research Center, Jaipur* did a case control study of Lp(a) levels in coronary heart disease in patients. They performed a case control study of 48 newly diagnosed coronary heart disease patients and 23 controls who were evaluated using clinical history and biochemical examination. Lipoprotein(a) was measured by quantitative latex-enhanced immunoturbidimetric method. Geometric means of biochemical parameters was obtained. Comprehensive lipid tetrad index was calculated using a previously validated formula. The mean lipoprotein (a) levels were significantly greater in cases (11.95±2.8mg/dl, range 1-102mg/dl) as compared to controls (6.68±3.4mg/dl, range 1-73mg%) (t=2.08, p=0.041). As compared to controls, in coronary heart diseases cases, mean lipoprotein (a) levels in patients upto 50yrs (10.27±2.8 vs

7.27±3.4mg/dl) as well as those above 50 yrs were significantly more ($p<0.05$). CAD patients had a significantly greater prevalence of Lpa levels, 20mg% of more ($p<0.05$).

Comprehensive lipid tetrad index was also slightly higher in cases (14688.2±3.6) than in controls (8358±4.36) ($t=1.68$ 1 tailed $p<0.05$). This study shows that lipoprotein(a) levels are significantly more in both younger and older CAD patients compared to controls.

Bhal VK, Vaswani M, Thatai D et al[22] did a plasma level study of apolipoprotein A1 and B in Indian patients with angiographically defined coronary artery disease and concluded that measurements of apo-A1 and apo-B were found to superior to traditional lipid measurements in identifying the presence of Cad in India.

Comperhensive lipid tetrad index

Recently , a comprehensive lipid tetrad index has been proposed by Enas as the best estimate of the

total burden of dyslipidemia. It is derived by the product of serum cholesterol, triglycerides, and Lp(a) values divided by the HDL level and may eliminate the need for various cut off points and ratio's involving these lipids. A high index indicates a highly atherogenic lipid profile and warrants aggressive treatment of all dyslipidemias.

Lipid tetrad index of Asian Indians are shown below:

Population	Index
Asian Indians in India-men	12,899
Asian Indians in India-women	10,814
Asian Indians in UK-men	20,692
Asian Indians in UK-women	15,615
Asian Indians CAD patients in UK	37,420
White CAD patients in the UK	18,085

MATERIAL AND METHODS

MATERIAL AND METHODS

This study has been conducted on 36 freshly diagnosed coronary artery disease patients presenting on first instance with first episode of freshly diagnosed acute myocardial infarction inclusion criteria were :

(a) All patients of acute myocardial infarction were freshly diagnosed and were not a known case of coronary artery disease.

(b) All patients found to have confounding factors for dyslipidemia were excluded from the study. (confounding factors included presence of systemic hypertension, diabetes mellitus, endocrine disorders, liver disease, kidney disease and history of intake of lipid profile affecting drugs).

(c) The diagnosis of myocardial infarction was made by combination of history, physical examination, ECG, Troponin T-test, cardiac enzymes and echocardiography. Patients having

evidence of old myocardial infarction on ECG were also excluded from the study.

Examination

History : Name, age, sex, weight, height, BMI, waist- hip ratio, whether smoker or not. Detailed history was taken to document family history of premature coronary artery disease, hypertension. Diabetes mellitus, obesity, familial hypercholesterolemia, intake of lipid profile affecting drugs. The history also included presence of any other systemic symptomatic atherosclerotic disease for example, transient ischemic attacks, leg claudication, xanthelesma, tendon xanthomas etc.

Physical examination : Patient's full general examination was done to look for any signs of hyperlipidemia, thyroid swelling etc. physical examination included :

- General built and nutrition
- Resting pulse-rate and BP and record of any abnormality detected.

- Detailed examination of cardiovascular system including any abonrmalities of heart sounds or presence of 3rd or 4th heart sound or any other abnormal sound.
- Detailed examination of all other systems also to rule out symptomatic atherosclerotic disease of other systems.
- Body weight, height, body mass index, waist hip ratio (to diagnose truncal obesity).

Investigations

General routine investigations

- Haemogram
- Total and differential count
- Fasting and 2hr post prandial blood glucose measurements to rule out diabetes mellitus.
- Liver function tests including SGPT, SGOT, S. bilirubin and S. Alkaline phosphate to rule out liver disease.

- Renal function tests including blood urea and serum creatinine to rule out renal disease.
- Routine urine microscopy was also done for all patients.

Cradiac investigations

- Resting 12 lead ECG on presentation and afterwards.
- Echocardiography was done for all patients to look for wall motion abnormalities.
- Cardiac enzymes like CPK-MB and or troponin-T test was also done when required.

Extended lipid profile : Fasting venous sample was taken for all patients within 12 hours of onset of chest pain for following lipid parameters.

Total cholesterol, LDL-cholesterol, triglycerides, HDL-cholesterol, VLDL, lipoprotein (a), apolipoprotein A1, apolipoprotein B, apolipoprotein A/apolipoprotein B ratio.

The blood sample obtained were sent with due precautions to LAL's Laboratory private Ltd., N.

Delhi, immediately for analysis. LAL's Laboratory Private Ltd. is approved by WHO and Center for Disease Control (CDC), Atlanta, Georgia, USA and is a laboratory of International repute.

Technique employed for lipid profile measurement at above laboratory :

Lipoproteins (a)	By later enhanced nephelometry
Apolipoprotein A1 & Apolipoprotein B	By Immunoturbimetry
Total cholesterol	By spectrophotometry
HDL cholesterol	By spectrophotometric lipoprotein electrophoresis
LDL cholesterol, VLDL	By spectrophotometry

Analysis : the results of extended lipid profile will be pooled and patterns of lipid abnormalities studied using relevant statistical methods.

OBSERVATIONS

OBSERVATIONS

This study was carried out in 36 patients of freshly diagnosed CAD presenting with acute myocardial infarction. Only those patients were included in the study who were normotensive, non diabetic euthyroid having normal hepatic and renal functions and were not previously on any drug treatment which favorably or unfavorably alter their lipid profile. All the sample were taken in fasting state within 12 hrs of onset of chest pain. Blood sample for extended lipid profile was sent to LAL's laboratory, N. Delhi with due precautions.

Table-1 Distribution of patients according to age group

Age group	No. of patients
<30 yrs.	1
30-39 yrs.	None
40-49 yrs.	8
40-59 yrs.	18
60-69 yrs.	7
70-79 yrs.	2
>80 yrs.	None

Percentage of female patients was 16.6%(6/36).

The average age of patients was 55.86yrs (25-78yrs).

Percentage of patients who were below 60 yrs was 75% (27/36).

Percentage of patients who were below 40 yrs was 2.77%(1/36).

Percentage of patients who were below 50 yrs was 25% (9/36).

The maximum clustering of acute myocardial infarction patient was seen in the age group range 40-59yrs which included 70.22% patients (26/36).

Percentage of Smokers : Of the 36 patients selected 15/36 (41.7%) were Bidi-smokers (>1 bundle/day), for at least 5yrs and 2 were tobacco chewer (5.55%).

Total cholesterol (mg%)

Table-2 Following classification of patients total cholesterol has been done

Total cholesterol (mg%)	No. of patients
<100mg%	None
100-119mg%	2
120-139mg%	4
140-159mg%	16
160-179mg%	11
180-199mg%	2
≥200mg%	1

The average total cholesterol in the study group was 155.9±21.05mg%. Maximum clustering of total cholesterol was seen in the range 140-159mg% in which values of 16 patients fell. Only 1/36 (2.9%) patients had total cholesterol >200mg%. The range of total cholesterol was 106-207mg%.

LDL cholesterol

Table-3 Following classification of LDL cholesterol has been done for patients values

LDL cholesterol (range in mg%)	No. of patients
50-74.9mg%	6
75-84.9mg%	6
85-94.9mg%	10
95-104.9mg%	9
105-114.9mg%	3
115-139.9mg%	1
≥140mg%	1

The average value of LDL cholesterol in the study group is 90.4±16.67mg%. 19/36 (52.8%) LDL-C values lie between range 85-104mg%. Percentage of patients having LDL-cholesterol value ≥100mg% requiring drug treatment according to National Cholesterol Education Programme of United States is 9/36 i.e. 25%. The range of LDL-cholesterol is 56.44-141mg%.

Triglycerides

Table-4 Values of triglycerides (in mg%) of patients of the study has been classified as under

Triglycerides (range in mg%)	No. of patients
50-79.9mg%	1
80-99.9mg%	2
100-119-9mg%	2
120-139-9mg%	6
140-159.9mg%	7
160-179.9mg%	5
180-199.9mg%	6
200-219.9mg%	4
220-239.9mg%	1
>240mg%	2

The average value of triglyceride in the study group was 164±51.74mg%. Percentage of patients having high triglycerides value i.e. ≥200mg% is 19.44%

(7/36). The range of triglycerides values was 67-354mg%.

HDL-cholesterol

Table-5 HDL changes for patients in the study group has been classified as

HDL-cholesterol (range in mg%)	No. of patients
<25mg%	2
25-29.9mg%	13
30-34.9mg%	7
35-39.9mg%	10
40-44.9mg%	1
45-49.9mg%	3
≥50	None

The average value of HDL-cholesterol in the study group was 33.0±6.5mg%. Percentage of patient having low HDL as independent risk factor for coronary artery disease (i.e. level <35mg%) was 61.11%(22/36). The range of HDL cholesterol was between 23-46.85mg%.

VLDL

Table-6 VLDL for patients in study group is classified as

VLDL (range in mg%)	No. of patients
<20mg%	3
20-29.9mg%	15
30-39.9mg%	11
40-49.9mg%	3
50-59.9mg%	4
≥60	None

The average value of VLDL in the study group was 32.6±10.9mg%. Percentage of patients having unfavorable VLDL levels >41mg% was 18.4(7/36). The range of VLDL cholesterol was 14.42-58.2mg%.

Lp(a)

Table-7 The Lp(a) for the study group has been classified as under

Lp(a) (range in mg%)	No. of patients
<10mg%	None
10-19.9mg%	16
20-29.9mg%	5
30-39.9mg%	11
40-49.9mg%	4
>50	None

The average Lpa for the patients in the study group was 24.9±10.29mg%. Percentage of patients having high Lpa levels (i.e. >30mg%) was 41.67%(15/36). The range of Lpa was 10.3-45.0mg%.

Apolipoprotein A1

Table-8 Apolipoprotein levels for the studied patients has been grouped as follows

Apolipoprotein (range in mg%)	No. of patients
<70mg%	3
70-79.9mg%	6
80-89.9mg%	8
90-99.9mg%	10
100-109.9mg%	7
≥110	2

The average Apolipoprotein A1 levels in the study group was 85±14.62mg%. The desirable Apolipoprotein A1 level is in the range 104-202mg%. *For our patients population percentage of patients having Apolipoprotein A1 less than 104mg% (i.e. desirable levels) is 86.11% (31/36).* The range of Apolipoprotein A1 is 59-110mg%.

Apolipoprotein B

Table-9 Apolipoprotein levels for studied population has been classified as

Apolioprotein-B (range in mg%)	No. of patients
<66mg%	1
66-74.9mg%	4
75-84.9mg%	9
85-94.9mg%	7
95-104.9mg%	10
105-114.9mg%	4
≥115	1

The average apolipoprotein B in the study group is 89±14.09mg%. The desirable range of apolipoprotein B is (66-133mg%). The range of apolipoprotein B was 59-118mg% in our study group.

ApoA1/ApoB ratio

Studies have shown that ApoA1:ApoB ratio distinguishes unequivocally between persons with and without CHD.

Table-10 Suggested risk levels for coronary heart disease

Risk	ApoA1:ApoB ratio
High	0.00-5.00
Moderate	.051-1.00
Average	1.01-1.50
Low	1.51-5.00

In our study group percentage of patients having unfavorable ApoA1 by Apo B ratio (<1.00) was 49.44%(16/36). None of the patient had this ratio in the high risk range i.e. 0.00-5.00. The ApoA1/ApoB ratio varied between 0.61-1.52.

Total cholesterol/HDL ratio

The ideal Total cholesterol/HDL ratio should be <5.00. For our study group this ratio varied between

2.75-9.0. Percentage of patients having undesirable Total cholesterol/HDL ratio (i.e. >5.00) was 36.11% (13/36).

LDL cholesterol/HDL cholesterol ratio

The desirable LDL/HDL ratio should be <3.55. *For our study group this ratio has varied between 1.55-6.13. Percentage of patients having unfavorable ratio (i.e. ≥3.55) was 11.11% (4/36).*

BMI

The BMI of the study group varied between 19.7-31.25. *The average BMI of the study group was 23.72. Percentage of patients who were overweight were (i.e. BMI>25) 22.2% (8/36).* Percentage of patients who were obese were (i.e. BMI>30) were 2.78% (1/36).

Comprehensive lipid tetrad index

As proposed by Enas as the best estimate of total burden of dyslipidemia. It is derived as follows :

$$\frac{\text{Total cholesterol} \times \text{Triglycerides} \times \text{Lpa}}{\text{HDL}}$$ (all in mg%)

$$= \frac{24.9 \times 164 \times 155.9}{33.01} = 19286$$

Rural/Urban classification

Of the study group, 23 patients were from rural background and 13 from urban background.

Percentage of patients of :

Rural background =63.88%

Urban background=36.11%

Waist hip Ratio

The waist hip ratio of the patient varied between 0.9-1.16.

The average waist hip ratio of the group was 0.99.

Percentage of patient having unfavorable waist hip ratio (truncal obesity i.e. >1.00) was 36.1% (13/36).

DISCUSSION

DISCUSSION

The present study has been carried out in Cardiology unit of Medicine Department on 36 freshly diagnosed acute myocardial infarction patients presenting in Intensive Coronary Care Unit Care had been taken by methods of detailed history, clinical examination and laboratory investigations to exclude those patients from the study who showed confounding factors for dyslipidemia other than coronary artery disease itself. Thus patients with documented Systemic hypertension, Diabetes Mellitus, kidney disease, hepatic disease, endocrine disease, patients who were taking lipid profile affecting drugs or were known patients of coronary artery disease previously ***were excluded from the study***. Informed consent was taken from each patient.

Table –1 shows distribution of patients according to age. *As can be seen from the table the average age of the patients was 55.86 yrs (25-78yrs).* Percentage of patients who were below 60yrs of age

was 75% (27/36). Percentage of patients who were below 40yrs was 2.77 (1/36). Percentage of patients who were below 50yrs was 25% (9/36).

It can also be seen from table-1 that maximum clustering of MI patients was seen in the age group range 40-59 yrs which included 70.22% of patients (26/36).

A study[19] *by Mammi MV, Parvitharan, Rehman A et al, 1990 at Calicut Medical College* found that percentage of acute MI patients below 40yrs was 17%. This figure has been 2.77% in our study possibly because of small sample size in our study. In their study they found out that 55% of the male patients of acute myocardial infarction were below 50yrs. This figure has been 25% in our study possibly because of same above reason. Percentage of patients below 55yrs in their study was 67%, Compared to 47.2% patients in our study. In comparison only 45% of the cases of MI and 15% of the cases of death from M! in the US occur in persons under 65yrs of age.

In our study the percentage of female patients was 16.66 (6/36). This is a relatively low figure the cause of which can be explained by the small sample size of our patient population and also lower incidence and reporting of MI in females of Bundelkhand region.

Percentage of smokers : Of the 36 patients selected 41.7% (15/36) were Bidi smokers (>1 bundle/day for atleast 5yrs) and 2 were tobacco chewer.

Studies conducted on Indian CAD patients who are settled in United States found that smoking is a less commoner risk factor for coronary artery disease in patients of Indian origin compared to whites[7].

A comparative study[12] of smoking found out incidence of smoking to be 35.8% in urban and 1.4% for urban females in North India. Corresponding figure for smoking for rural males and females was 54.7% and 24.3% respectively in the same study.

Table-2 shows classification of patients of our study according to their total cholesterol. In our study the average total cholesterol of patients was 155.9±21.05mg%. Maximum clustering of total cholesterol values was seen in the range 140-159mg% in which values of 16/36 patients fell. Only 2.9% patient (1/36) had cholesterol value in excess of 200mg%. The range of total cholesterol seen was 106-207mg%.

Krishnaswamy[5] *et al* in his study of lipid profile of 877 CAD patients found mean total cholesterol in CAD patients to be 209.54±47.92mg%, compared to 155.9±21.05mg% in our study.

A study[6] *by Gupta R, Kaul V, Prakash H, Sarna M, Singhal S, Gupta VP at Monilek Hospital and Research Centre, Jaipur in 2001* of lipid abnormalities in coronary heart disease patient found that levels of total cholesterol was not significantly higher in CAD patients compared to healthy age-matched controls. This finding is in conformity with our observation as we also did not

find total cholesterol to be markedly raised in our patient population.

A study[7] conducted at Louisiana State University Medical College Centre, New Orleans, USA for risk factors for Coronary Artery Disease and levels of lipoprotein(a) in Asian Indians of USA found average total cholesterol to be 218.88±39.0mg%, compared to 155.9±21.05mg% for our study.

A study[7] of dyslipidemia in young North Indian patients of coronary heart disease conducted at AIIMS, N. Delhi found total cholesterol value in CAD patients on an average to be 220.9±50mg% compared to 167.8±57.0 in healthy controls.

Table-3 shows LDL-cholesterol values for our study group. *The average value of LDL-cholesterol in the study group was 90.4±16.67mg%.* 52.8% (19/36) patient had their LDL-C value falling in the range 85-104mg%. Percentage of patients of MI having LDL-cholesterol value ≥100mg% requiring drug treatment according to NCEP guidelines was

25%(9/36). The range of LDL-C seen was 56.4-141.0mg%.

Comparison with other studies of LDL-cholesterol levels in CAD patients, a *study*[6] *conducted at Monilek Hospital and Research Centre, Jaipur*, which was population based case control found that level of LDL-C was not significantly higher in CAD patients when compared to normal healthy age matched controls.

A study[7] *of risk factor for coronary artery disease in Asian Indians of USA* found average LDL-cholesterol to be 117.8±35.1mg% compared to 90.4±16.67mg% in our study. This study was conducted on 110 Asian Indian Physicians residing in United States.

A study[8] *of dyslipidemia in CAD patients conducted at AIIMS, in 2000* found LDL-cholesterol average value among CAD patients to be 152±47.0mg% compared to 90.4±16.67mg% in our study

One more study[9] *of lipid-profile conducted on Urban population in Thiruvananthapurum* found average LDL-cholesterol to be 145.9±41.0mg%.

From all of the above studies the conclusion derived in reference to our study is that our population of CAD had lower average LDL-cholesterol values. The above finding can be explained on the basis of two reasons. Firstly that in our study we had ruled out all confounding factors for dyslipidemia except the CAD itself. Second reason could be because of small sample size of our patient population.

Table-4 shows values of triglycerides (in mg%) in the patients of study group. The average value of triglyceride in the study group was 164±51.74mg%. Percentage of patients having high triglyceride value i.e. >200mg% was 19.44% (7/36). The range of triglyceride values was 67-354mg%.

A study by Austin[4] *et al* recently described an atherogenic lipoprotein phenotype B characterised by moderate hypertriglyceridemia, a high proportion

of small dense LDL, a high level of apolipoprotein B and a low level of apolipoprotein A1 and HDL. It can be inherited as a single gene trait. Atherogenic phenotype B can be differentiated from benign phenotype A by simple measurements of S. triglycerides and HDL. A triglyceride value of 95mg/dl discriminates the two phenotypes in 83% cases, whereas an HDL value of 39mg/dl separates the 2 groups in 72% of cases. When a triglyceride level of >95mg/dl was used, 75% of Asian Indian men in the *Coronary Artery Disease Among Indians Study* demonstrated this phenotype. This figure when using S. tyriglyceride >95mg% with HDL-C <35mg% to identify atherogenic phenotype B was found to be 91.8% in our study.

A study be Krishnaswamy[5] et al at CMC Vellore of lipid levels in Indian patients with coronary artery disease, took 871 cases of angiographically proven CAD patients. In this study he found mean S. triglyceride levels in CAD patients to be

174.05±83mg%. The corresponding figure of 164±51.74mg% in our study is quite comparable.

A study[6] *of lipid abnormalities in coronary heart disease, a population based case- control study at Monilek Hospital and Research Centre, Jaipur* found following values of S. triglycerides in CAD patients in different age groups.

Age group S. Levels(in mg%)

40-49yrs- 193.3±96 vs 152.8±78 in healthy controls

50-59yrs- 176.7±76 vs 162.9±97 in healthy controls

60-69yrs- 175.5±93 vs 148.1±65 in healthy controls

>70yrs- 170.8±20 vs 149.9±9($p<0.05$) in healthy controls

A study[8] *of dyslipidemia in young North Indian patients with CAD at AIIMS* found the mean level of S. triglyceride in CAD patients to be 110.8±33.8mg% vs 95.5±32.0mg% in healthy controls.

Another study[7] *of risk factors for coronary artery disease in 110 Asian Physicians living in USA* found

the average value of S. triglyceride to be 133.35±41.5mg%.

A study conducted on CAD patients in US found average S. triglyceride value to be 190±142mg/dl in white population. It is clear from above studies that study total triglyceride levels in our population was lesser compared to white CAD patients, probably explained because of the reason that we had excluded al confounding factors for dyslipidemia except the CAD itself.

Table-5 shows values of S.HDL cholesterol for the patient group. *The average value of HDL cholesterol in the study group is 33.0±6.5mg. Percentage of patients having low HDL as independent risk factors for coronary artery disease (i.e. level <35mg%) was 61.11% (22/36).* The range of HDL cholesterol observed was 23-46.85mg%.

Comparison with other studies

Asian Indians who had migrated to United States were recently surveyed as part of Coronary Artery Disease Among Indians Study. In this study Asian

Indians were found to have significantly higher prevalence of diabetes mellitus, hypertriglyceridemia and lower serum levels of HDL-C, but lower prevalence of cigarette smoking, systemic hypertension, family history of premature CAD and obesity, compared with Framingham Offspring study. Only 14% of Asian Indian men and 5% of Asian Indian women had optimal HDL in the *Coronary Artery Disease Among Indians Study* (optimal HDL>52mg% for men and >66mg% for women).

A population based case control study of lipid abnormalities in coronary heart disease at Monilek Hospital and Research centre, Jaipur, which had recruited 635 newly diagnosed patients with coronary heart disease found average value of HDL cholesterol in the patient group to be as follows.

Age group	value(in mg%)
30-39yrs	35.1±11
40-49yrs	39.0±10
50-59yrs	38.9±11
60-69yrs	38.6±11

All the above values of HDL-C are comparable to HDL-C values of our study.

A study of dyslipedemia in young North Indian patients Coronary Heart Disease found the levels of HDL cholesterol to be 39.3±5.9mg%.

Another study of risk factors for CAD in 110 Asian Indian physicians residing in USA found average level of HDL-C to be 40.6±9.45mg%.

From all of the above studies it is clear that low HDL (i.e.<35mg%) is a very important risk factor for CAD in our patient population, the finding which is seen in 61.11% patients (22/36).

Table VI- Shows value of serum VLDL in the patient subgroups. *The average value of VLDL in the study group was 32.6±10.9mg%.* Percentage of patients having unfavorable VLDL levels (i.e. >41mg%) was 18.4% (7/36). The range of VLDL cholesterol noticed was in the range 14-42mg%.

Table-7– Shows values of Lpa (lipoproteins(a)) for the patients classified in different range of

values. *The average level of lipoprotein (a) for the patients in the study group was 24.9±10.29mg%. Percentage of patients having high Lp(a) levels (i.e. >30mg%) was 41.67% (15/36).* The range of Lpa observed was 10.3-45.0mg%.

Recent studies[4] indicate that elevated lipoprotein (a) levels are strong predictors of CAD. Lipoprotein (a) levels may be related to both atherogenesis and thrombosis and may be a key link between lipids and thrombosis. The levels of lipoprotein (a) were found to be three times higher in the Asian Indians than in Chinese in Singapore. The *Coronary Artery Dsease Among Indians Study* also demonstrated higher levels of lipoprotein (a) among Asian Indians in United States than among whites.

A case control study[10] of S. lipoprotein (a) in Coronary Heart Disease patients conducted at Jaipur and Illinois USA, found that lipoprotein (a) levels were significantly higher in cases compared to controls (11.95±2.98mg/dl vs 6.68±3.4mg%). The average value of Lp(a) found in this study was

considerably lower than values found in our study ((24.9±10.29mg%), the finding which could be explained on the basis that as Lp(a) levels are genetically determined there are wide variations in Lp(a) levels in different patient subgroup of different regions.

A study of lipoprotein (a) levels of 110 Asian physicians residing in United States found average value of Lp(a) to be 18.5±20.0mg%. This value of Lp(a) is quite in agreement to values of Lp(a) found in our study 24.9±10.29mg%. In the same study levels of Lp(a) (mean=20.0mg/dl) among Indian population were comparable to findings of Lp(a) values of Asian Indians in Singapore (20.1mg%). The Lp(a) levels and high percentage Lp(a) (>30mg%) in males from this study (18.5mg% and 20%) were also comparable to findings from male Indian physicians who migrated to US (19.6mg% and 24% respectively). When compared to two population based studies, mean level of Lp(a) (20mg%) in Indian lay between USA whites (15-

17mg%) and USA blacks (31-34mg%) and was two fold of Mexicans (11mg%). This study[7] showed that Asian Indians have higher levels of Lp(a) than USA whites and that Lp(a) is a possible risk factor for CAD in the Asian Indians.

Table-8 and 9 shows Apolipoprotein A1 and Apolipoprotein B values in the study group. *The average apolipoprotein A1 levels in the study group was 85±14.62mg/dl* (desirable range of ApoA1= 104-202mg%). For our patient population percentage of patients having Apolipoprotein A1 less than desirable level of 104mg% was 86/11% (31/36). The range of Apolipoprotein A1 observed was 68-110mg%.

The average *Apolioprotein B in the study group was 89±14.09mg%.* The desirable range of Apolipoprotein B is 66-133mg%. The range of Apolipoprotein B observed was 59-118mg%.

In our study group percentage of patients having unfavorable ApoA1/ApoB ratio (i.e.<100) was 49.44% (16/36). None of the patient had this ratio in

the high risk range i.e. 0.00-0.50. The variation observed in ApoA1/ApoB ratio was 0.61-1.52.

Studies have shown that ApoA1:ApoB ratio distinguishes unequivocally between persons with and without CHD. Therefore, apolipoprotein A1 and B studies are superior to conventional total cholesterol, HDL and LDL cholesterol studies for predicting risk for atherosclerosis.

A study[7] *of 110 Asian Physicians residing in USA* for risk factors for coronary Artery disease found average level of apolipoprotein A1 and B to be 131±24 and 147±28mg% respectively. The composite ApoA1/ApoB ratio for this population group was 0.89 which is comparable to ApoA1 by ApoB ratio obtained in our study i.e. 0.95.

A study conducted on lipid profile of patients with microvascular angina in Greece found the average level of apolipoprotein B to 146±32mg/dl in patients of CAD (vs 89±14.09mg% in our study).

Hence we conclude by saying that although the absolute values of Apolipoprotein A1 and

Apolipoprotein B were higher in above two studies the more important discriminator of severity of atherosclerosis i.e ApoA1/ApoB ratio was comparable to value found in our study.

Total Cholesterol/HDL ratio

The ideal Total Cholesterol/HDL ratio should be <5.00. For our study group this ratio varied between 2.75-9.0. *Percentage of patients having undesirable total cholesterol/HDL ratio (i.e.>5.00)was 36.11% (13/36).*

LDL cholesterol/HDL ratio : The desirable LDL-C/HDL-C ratio should be <3.55. For our study this ratio varied between 1.55-6.13. Percentage of patients having unfavorable ratio (i.e.>3.55) was only 11.11% (4/36).

Patients of microvascular angina in a study[16] *conducted in Greece* were found to have LDL/HDL ratio for CAD patients to be 4.1±1.5.

A study[6] *conducted on 110 Asian Indian Physicians residing in USA found,* Total/HDL ratio

and LDL-C/HDL-C ratio to be 5.15 and 3.44 respectively. It is clear that both above ratios are unfavorable (i.e. >5.00 and >3.55 respectively).

BMI

The body mass index (BMI) of the study group varied between 19.7-31.25. *The average BMI of the study group was 23.72.* Percentage of patients who were overweight were (i.e. BMI>25) was 22.2% (8/36). Percentage of patients who were obese (i.e. BMI >30) was 2.78% (1/36).

Waist Hip Ratio

The waist hip ratio of the patient varied between 0.91-1.16. *The average waist hip ratio of the group was 0.99.* Percentage of patients having truncal obesity (apple type obesity i.e. ratio >1.00) was 36.11 (13/36).

Comprehensive lipid tetrad index

Comprehensive lipid tetrad index has been proposed by ENAS[17] as the best indicator of total burden of dyslipidemia. It is derived by the product

of the total cholesterol, triglycerides and Lp(a) values divided by HDL. This value for our population subgroup is 19286.

Comparison of comprehensive of lipid tetrad index[17]

Our study	-	19286
Asian Indians in India men	-	12,814
Asian Indians in India women	-	10,814
Asian Indian in CAD patient in UK	-	37,420
White CAD patients in UK	-	18,085

Another case control study[10] *on CAD patients conducted in Jaipur and Illinois USA* found that comprehensive lipid tetrad index was 14468 for cases and 8358 for controls.

The comprehensive lipid tetrad index found in our study tallies with the found in above study (19286 vs 14468).

CONCLUSIONS

CONCLUSION

Following conclusion can be derived from our study :

1. Total cholesterol and LDL-cholesterol values are within normal range for most of the patients (average 155.9±21.05mg% and 90.4±16.7mg% respectively).

2. The major abnormality found in the extended lipid profile of the patients of myocardial infarction was high triglyceride, low HDL, high Lp(a) and high incidence of unfavorable ApoA1 by ApoB ratio (i.e. ratio <1.00).

3. Patient having atherogenic phenotype B as described by Austin[4] and defined as serum triglyceride value >95mg% and HDL-C values <35mg% was found in 60.1% patients (22/36).

4. Percentage of patient having high Lp(a) values was 41.66%.

5. Percentage of patient having unfavorable ApoA1/ApoB ratio (i.e. <1.00) was 91.8.

6. Comprehensive lipid tetrad index as defined by Enas[17] was 19286.

7. Unfavorable Total cholesterol by HDL ratio (i.e >5.00) was found in 36.11% (13/36) of patients.

8. Unfavorable LDL-C by HDL-C ratio (i.e. >3.55) was found in 11.11% (4/36) patients.

9. Percentage of patients who were overweight (BMI>25) was 25% (9/36).

10. Percentage of patients who had objective evidence of truncal obesity (i.e. waist hip ratio >1.00) was 36.11 (13/36).

11. Percentage of female patients was 16.6% (6/36).

12. Patients of myocardial infarction had average age of 55.86yrs. Percentage of patients who were below 50yrs was 25 (9/36). Maximum percentage of myocardial infarction patients was seen in the age group 40-59yrs which included 70.22% patients (26/36).

13. Rural Urban division of the patients was as follows :

    Rural background -63.88% (23/36)

    Urban background -36.11% (13/36)

14. Percentage of smokers in the study group was 41.7% and percentage of tobacco chewer were 5.6%.

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